Alternative Therapies for Treatment of Syphilis

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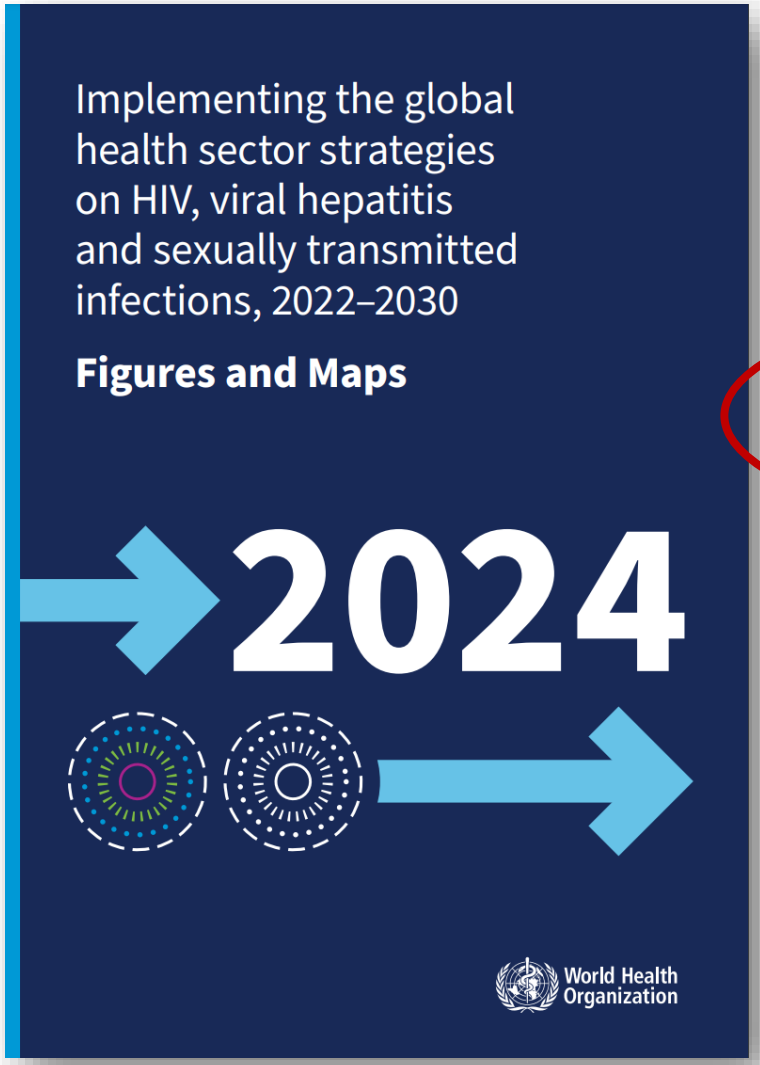
September 25, 2024

2024 WHO Situation Report on HIV, Viral Hepatitis, and Sexually Transmitted Infections



Global statistics

~1.3M new HIV infections & 630,000 related deaths
- Higher incidence among MSM, IDUs, sex workers, transgenders, people in prisons

~8M new syphilis cases among adults (15-49yrs)
- Estimated increases in congenital syphilis
- 220,000 syphilis-associated deaths

>1M infections daily of four curable STIs
- *Syphilis, gonorrhea, chlamydia, and trichomoniasis*

>80 countries reporting gonorrhea antimicrobial resistance

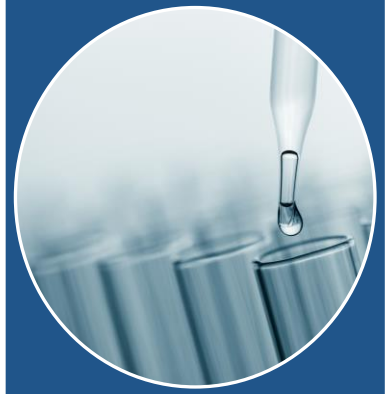
~1.2M new hepatitis B and ~1M new hepatitis C cases
- 1.3 million deaths associated with viral hepatitis

Slide source: J. Marrazzo

NIAID Research to Address Surging Syphilis Rates

New funding opportunity: RFA-AI-24-045

- Promoting Innovative Research in *Treponema pallidum* Pathogenesis.



Rapid POC Diagnostics: RFA-AI-23-039

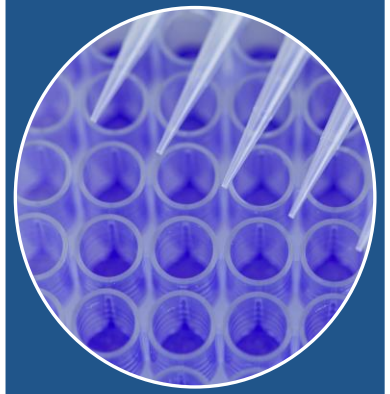
- Aimed at developing rapid point-of-care diagnostics *T. pallidum*.

Syphilis Specimen Collection

- Study enrolling volunteers at all stages of infection to develop biorepository to assist with development of diagnostics.

Syphilis in Pregnancy Study (SIPS)

- Monitoring outcomes of pregnant people diagnosed with and treated for syphilis, and infant health outcomes.



STI Cooperative Research Centers

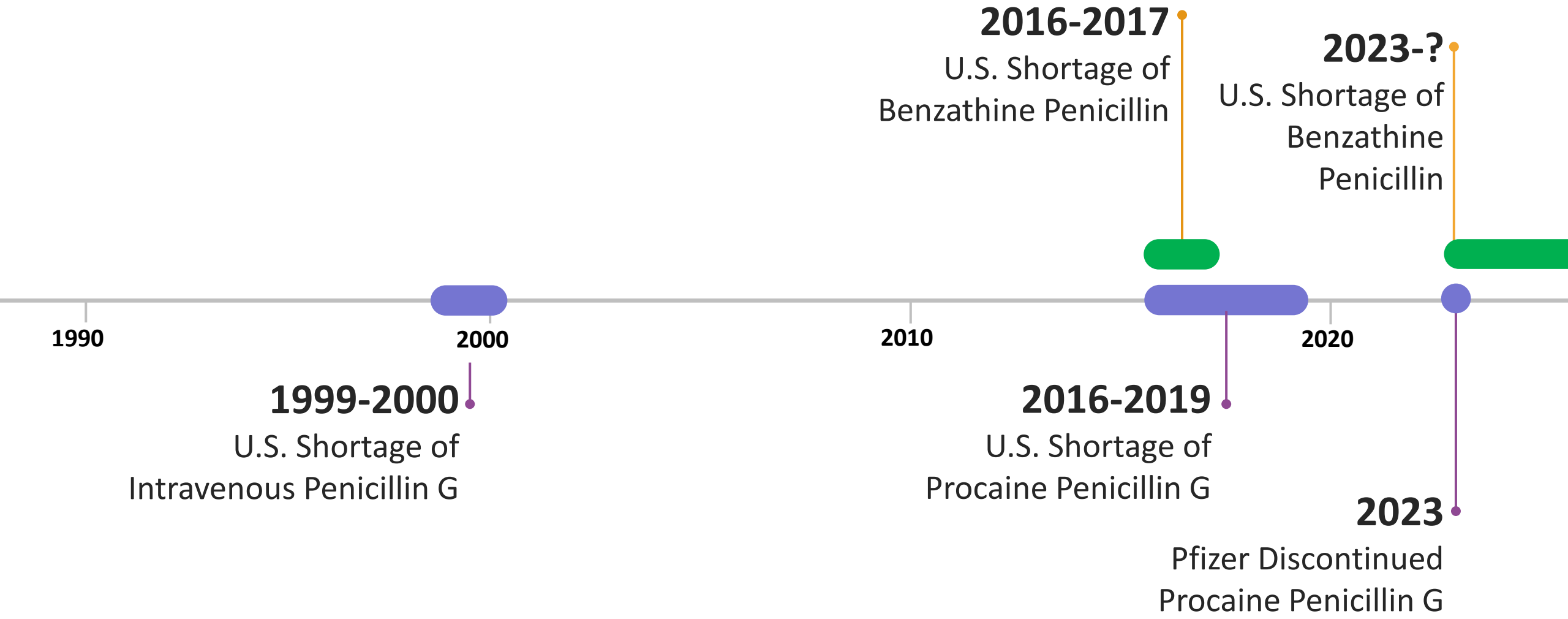
- Investigating the structure of outer membrane proteins of *T. pallidum* as potential vaccine targets.

Small Business Contract Proposals

- Solicited SBIR proposals aimed at identifying alternatives to BPG treatment.

Slide source: J. Marrazzo

Penicillin Shortages Have Been More Common in Recent Years



Credit: L Bachmann, CDC

Note: Shortage dates were based on CDC DCLs to the field except for the 1999-2000 shortage. The 1999-2000 shortage resolution year was based on media articles.

One vs 3 doses of BPG

JOURNAL ARTICLE

2889. One vs Three Weekly Doses of Benzathine Penicillin G for Treatment of Early Syphilis in Persons with and without HIV: A Multicenter Randomized Controlled Trial (RCT)

Edward W Hook, III, FIDSA, Kimberly Workowski, MD, Jodie A Dionne, MD, MSPH, Candice J McNeil, MD, MPH, Stephanie N Taylor, MD, Batteiger Teresa, MD, Julia C Dombrowski, MD, MPH, Kenneth H Mayer, MD, MPH, Arlene C Seña, MD, MPH, Harold C Wiesenfeld, MD, CM, Charlotte Perlowski, MSPH, Lori Newman, MD, Chunming Zhu, Ph. D, Jorge E Mejia-Galvis, MD, MBA

Conclusion:

- Treatment of persons with early syphilis with more than a single dose of 2.4 million units of BPG offers no therapeutic benefit irrespective of HIV infection status and was associated with increased rates of injection site discomfort.
- Presented as an abstract at ID Week 2023

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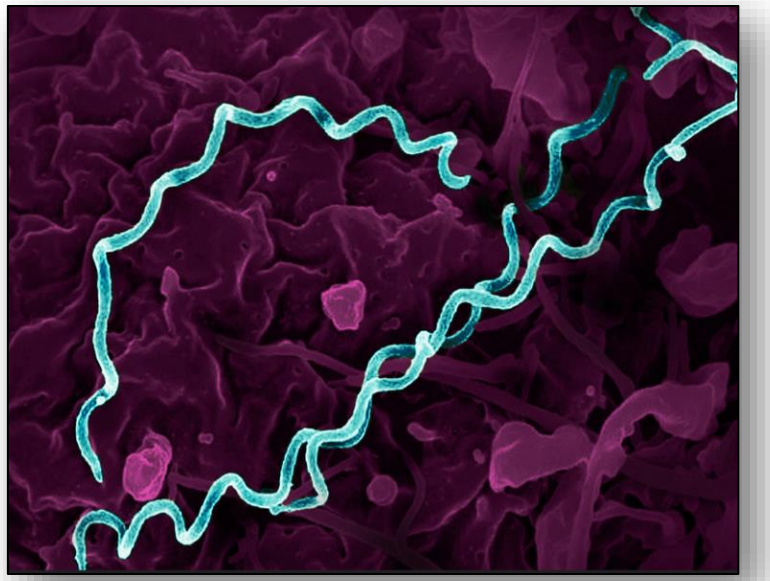
NIAID Syphilis Workshop: Alternative Therapies

- In February 2024, NIAID convened a workshop on alternative therapies to BPG for the treatment of adult syphilis, neurosyphilis, and syphilis in pregnant persons and infants.

- Topics included preclinical evaluation of candidate drugs, the potential need for studies on how candidate drugs are processed in the body during pregnancy, and how to approach clinical trials of treatment for congenital syphilis.



Colorized electron micrograph of *Treponema pallidum*. Credit: NIAID

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Alternative Antibiotics for the Treatment of Syphilis

- Alternatives to penicillin are needed
- WHO-sponsored Phase 2 trial to evaluate the efficacy of cefixime in the treatment of active syphilis among non-pregnant women
- Results will inform a proposed randomized controlled trial to evaluate cefixime as an alternative treatment for pregnant women with active syphilis and to evaluate prevention of congenital syphilis

BMC Infectious Diseases

BMC Infect Dis. 2020; 20: 405.
PMCID: PMC7288542
Published online 2020 Jun 10. doi: 10.1186/s12879-020-04980-1
PMID: 32522244

Phase II trial evaluating the clinical efficacy of cefixime for treatment of active syphilis in non-pregnant women in Brazil (CeBra)

Melanie M. Taylor,[✉1,2] Edna Oliveira Kara,[1] Maria Alix Leite Araujo,[3] Mariangela Freitas Silveira,[4] Angelica Espinosa Miranda,[5] Ivo Castelo Branco Coelho,[6] Maria Luiza Bazzo,[7] Gerson Fernando Mendes Pereira,[8] Silvana Pereira Giozza,[8] Ximena Pamela Díaz Bermudez,[9] Maeve B. Mello,[9,10] Ndema Habib,[1] My Huong Nguyen,[1] Soe Soe Thwin,[1] and Nathalie Broutet[1]

Trial evaluating the clinical efficacy of cefixime for treatment of active syphilis in non-pregnant women in Brazil - CeBra Study


Taylor et al. BMC Infectious Diseases (2020) 20:405
https://doi.org/10.1186/s12879-020-04980-1

BMC Infectious Diseases

STUDY PROTOCOL Open Access

Phase II trial evaluating the clinical efficacy of cefixime for treatment of active syphilis in non-pregnant women in Brazil (CeBra)

Melanie M. Taylor[1,2*], Edna Oliveira Kara[1], Maria Alix Leite Araujo[3], Mariangela Freitas Silveira[4], Angelica Espinosa Miranda[5], Ivo Castelo Branco Coelho[6], Maria Luiza Bazzo[7], Gerson Fernando Mendes Pereira[8], Silvana Pereira Giozza[8], Ximena Pamela Díaz Bermudez[9], Maeve B. Mello[9,10], Ndema Habib[1], My Huong Nguyen[1], Soe Soe Thwin[1] and Nathalie Broutet[1]

- **Study design**: Randomized, non-comparative phase 2 efficacy trial
- **Population**: non-pregnant women (ages 18 and over) diagnosed with active syphilis (RPR titers ≥1:16)
- **Randomization:** 140 cefixime and 70 penicillin
- **Follow up:** 15 days, 3, 6 and 9 months following treatment with cefixime 400mg orally twice a day for 10 days

Primary objective: To demonstrate the efficacy of Cefixime, as measured by a 4- fold decrease in Rapid Plasma Reagin (RPR) titer from baseline up to 6 months after treatment

Secondary objective: To determine the drug safety, during or after treatment with Cefixime and the tolerability of the regimen.

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Slide source: Melanie Taylor

Repurposing Drugs for Treatment of Syphilis: Clinical Trials

- **Linezolid vs BPG for treatment of early syphilis:** (PI: Oriol Mitja Villar)
  - The Trep-AB clinical trial will test the efficacy of Linezolid (LZD), compared to standard treatment, Benzathine penicillin G (BPG), for early syphilis in humans.
  - One arm of the trial compared oral linezolid (600 mg daily for 5 days) to BPG, however, this arm was discontinued due to futility.
  - The second arm of this study is continuing to test oral linezolid (600 mg twice daily for 10 days).
  - Study Completion estimated: December 2025

THE LANCET
Infectious Diseases

Oral linezolid compared with benzathine penicillin G for treatment of early syphilis in adults (Trep-AB Study) in Spain: a prospective, open-label, non-inferiority, randomised controlled trial

Maria Ubals, MD [a,g,h] · Patricia Nadal-Baron, MSc [g,i,*] · Maider Arando, PhD [j,*] · Ángel Rivero, MD [b,k] · Adrià Mendoza, MD [a,b] · Vicent Descalzo Jorro, MD [j] · Dan Ouchi, MSc [b] · Clara Pérez-Mañá, PhD [c] · Marlene Álvarez, PhD [d] · Andrea Alemany, MD [a] · Yannick Hoyos-Mallecot, PhD [i] · Ethan Nunley, BS [m] · Nicole A P Lieberman, PhD [m] · Alexander L Greninger, MD PhD [m,n] · Cristina Galván-Casas, PhD [b,o] · Clara Suñer, PhD [a,b] · Camila G-Beiras, PhD [a] · Roger Paredes, PhD [b,e,f,p,q] · Prof Alicia Rodríguez-Gascón, PhD [r,s] · Andrés Canut, MD [s,t] · Prof Vicente García-Patos, PhD [h] · Prof Magí Farré, PhD [c] · Michael Marks, PhD [u,v,w] · Lorenzo Giacani, PhD [l] · Martí Vall-Mayans, PhD [a,†] · Oriol Mitjà, PhD [a,b,†] ✉ Show less

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Repurposing Drugs for Treatment of Syphilis: Clinical Trials

- **Doxycycline compared to penicillin for treatment of neurosyphilis and ocular syphilis** (PI: Matt Golden and Ken Mayer)
  - Protocol in Development: Randomized trial to NIH to evaluate oral doxycycline as a treatment of neuro and ocular syphilis
  - A two arm non-inferiority trial is likely the best design
  - Why doxycycline?
    - Good experience with uncomplicated syphilis
    - Pharmacokinetic data suggest that doxycycline levels in the CSF and aqueous humor should be adequate to treat neurosyphilis
    - Clinical data on the efficacy of doxycycline in treating neurosyphilis are limited
    - UK and German guidelines recommend doxycycline as an alternative therapy for neurosyphilis

Slide courtesy of Matthew Golden/ University of Washington

Gaps Identified at the Workshop

- Gaps in knowledge regarding the effectiveness indices for *T. pallidum* pose a continuing challenge to the application of these approaches for therapeutic optimization.
- Enhancing the sensitivity and specificity of syphilis testing
- The integration of advanced diagnostics into clinical practice, especially in the form of rapid, point-of-care tests, could revolutionize syphilis screening and treatment.
- Significant gaps remain in our understanding of syphilis, particularly regarding how social determinants of health impact disease transmission and treatment efficacy.
- More data are needed on the long-term outcomes of newer treatments and therapies, especially for late-stage syphilis and immunocompromised populations.
- Exploring shorter, more effective treatment regimens could enhance adherence to syphilis treatment.
- **Other clinical trial concepts under discussion**: Amoxicillin +/- probenecid for early-stage syphilis; BPG for high titer latent syphilis of unknown duration (vs BPG x 3 sequential doses)

FY24 SBIR Contract Topic

Alternatives to Benzathine Penicillin for Treatment of Syphilis

- **Significance**: There are several barriers that limit use of injectable benzathine penicillin for syphilis treatment (not available orally; limited manufacturing facilities).
- **Purpose:** To support preclinical development of lead candidates for syphilis indications or repurposing of drugs to be more suitable for syphilis treatment
- Proposals have been received and are being evaluated

https://sam.gov/opp/f76f86b1206b4b6e9132c6cf9da3b6c0/view

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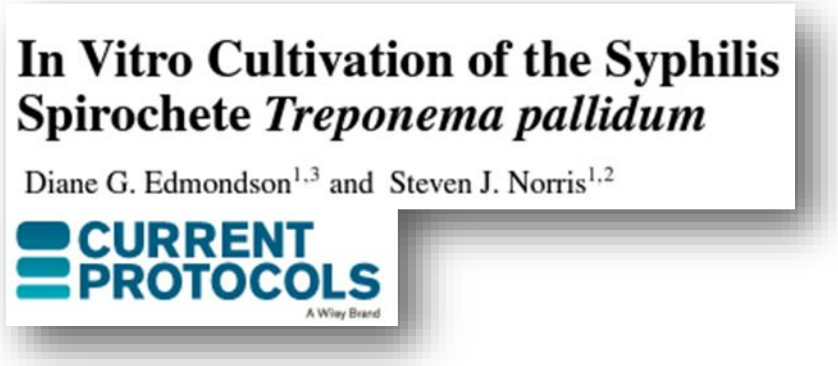
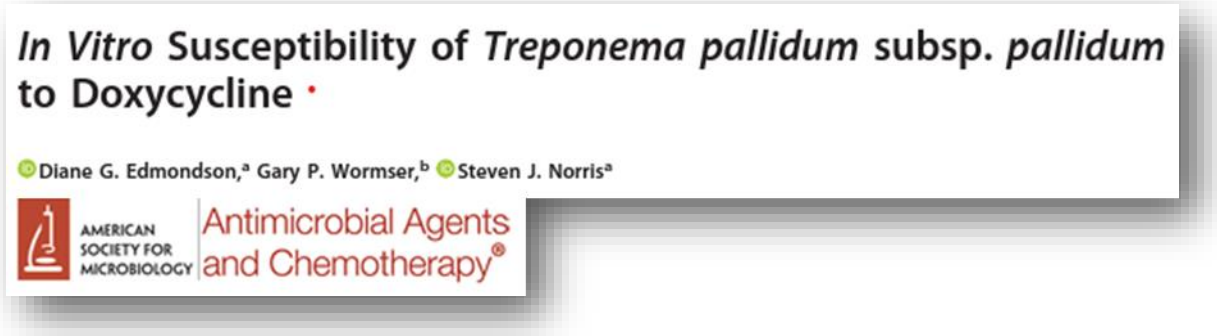
In vitro Culture and MIC testing of *Treponema pallidum*





- Detailed protocol published for long-term *in vitro* culture of *T. pallidum*
  - Until this breakthrough, cultivation required rabbits or other laboratory animals
- *In vitro* growth has also allowed for the development of an MIC assay that can be used to evaluate efficacy of new therapeutics

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7986111/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7508625/

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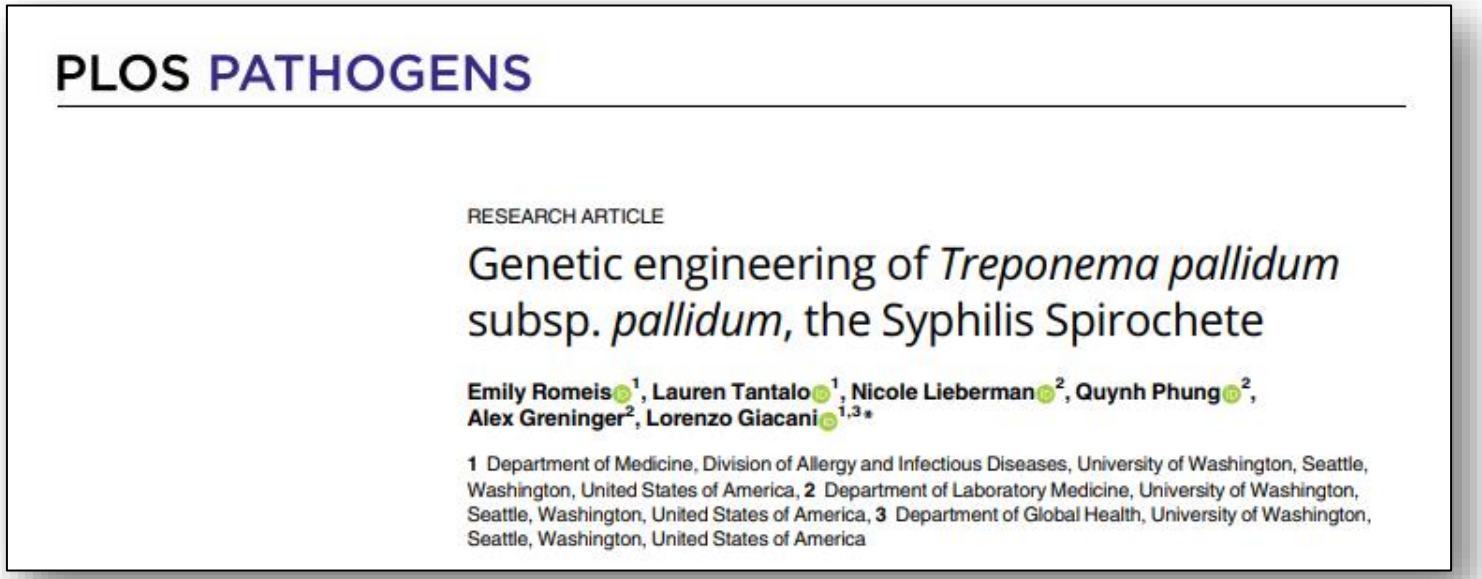
Genetic engineering of *Treponema pallidum*



PLOS PATHOGENS

RESEARCH ARTICLE

Genetic engineering of *Treponema pallidum* subsp. *pallidum*, the Syphilis Spirochete

Emily Romeis[1], Lauren Tantalo[1], Nicole Lieberman[2], Quynh Phung[2], Alex Greninger[2], Lorenzo Giacani[1,3]*

1 Department of Medicine, Division of Allergy and Infectious Diseases, University of Washington, Seattle, Washington, United States of America, **2** Department of Laboratory Medicine, University of Washington, Seattle, Washington, United States of America, **3** Department of Global Health, University of Washington, Seattle, Washington, United States of America

- Despite more than a century of research, genetic manipulation of T. pallidum), the causative agent of syphilis, has not been successful
- This research demonstrated that genetic manipulation of T. pallidum is attainable.
- This discovery will allow the application of functional genetics techniques to study syphilis pathogenesis and improve syphilis vaccine development.

https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1009612

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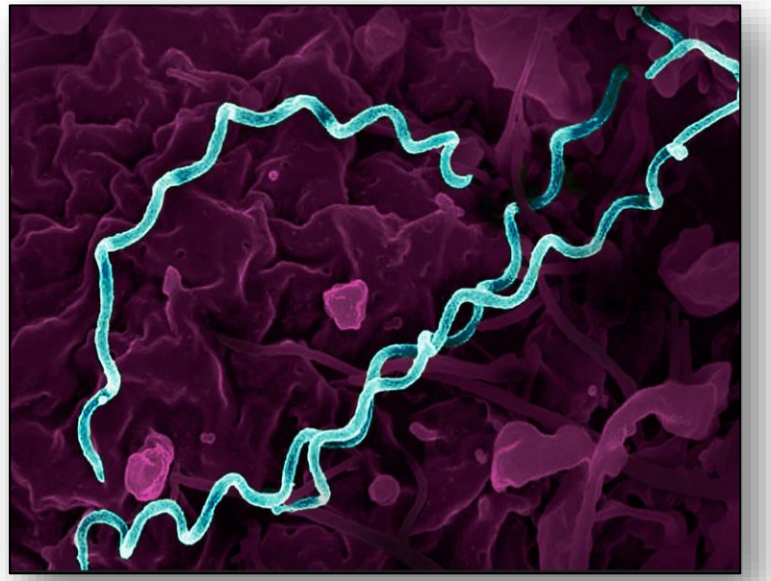
Chembio Dual-Path Platform (DPP): HIV/Syphilis Diagnostic

- FDA Approved: October 8, 2020
- Dual rapid test, detects antibodies:
  - HIV 1/2 and *Treponema pallidum*
- Sample specimens:
  - fingerstick whole blood
  - venous whole blood
  - plasma specimens
- Time to results: 15 minutes!

National Institute of Allergy and Infectious Diseases

Advancing *T. pallidum* Diagnostics

- **RFA-AI-23-039**: Advancing Development of Diagnostics for Congenital and Adult Acquired Syphilis
- Focus on:
  - Advancing new technologies
  - Ultra sensitive detection
  - Differentiating current and previous infections
    - Multi-omic approaches, genome and amplicon sequencing
  - Congenital syphilis diagnosis
    - Immune signatures, protein breakdown products, biomarkers
  - Diagnosis in point-of-care settings using variety of sample types including blood and ulcer swabs



Colorized electron micrograph of *Treponema pallidum*. Credit: NIAID

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New Awards: Syphilis Diagnostics

NEWS RELEASES

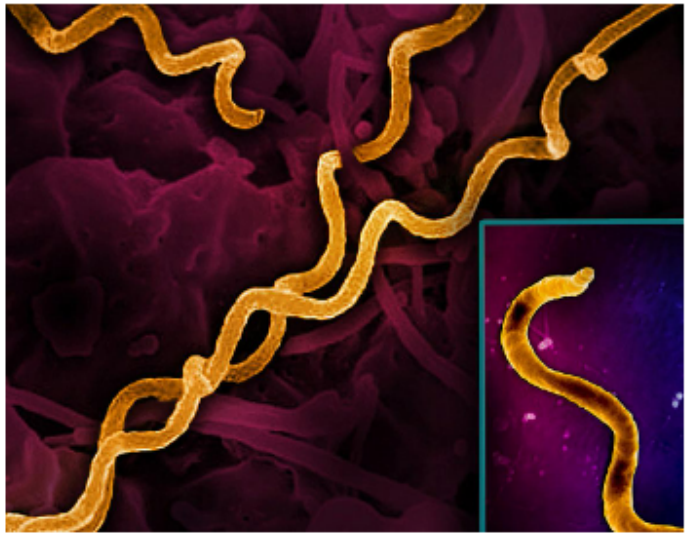
Tuesday, September 3, 2024

NIH awards will support innovation in syphilis diagnostics

Initiative to simplify testing process for an accelerated public health response,

The National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) has awarded grants for 10 projects to improve diagnostic tools for congenital and adult syphilis—conditions currently diagnosed with a sequence of tests, each with limited precision. The Centers for Disease Control and Prevention (CDC) estimates that adult and congenital syphilis cases increased by 80% and 183% respectively between 2018 and 2022—a crisis that prompted the U.S. Department of Health and Human Services (HHS) to establish a national taskforce to respond to the epidemic.

"Syphilis antibiotics work, but antiquated testing makes it very difficult to ensure that people are appropriately diagnosed and fully treated," said NIAID Director Jeanne M. Marrazzo, M.D., M.P.H. "Advanced diagnostics could streamline syphilis care and also enhance our ability to measure the efficacy of candidate syphilis vaccines and other prevention modalities."



Electron micrograph imagery of Treponema pallidum, the bacteria that cause syphilis, including a foreground close-up of a single particle (right). Spiral-shaped bacteria are colorized in gold. *NIAID*

Ongoing Public Health Needs: New Interventions for the Future!

Thank You

DMID/ESTIB/STI Section Team
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